**Briefing Memo on West Nile Virus (WNV) Infection and Laboratory Diagnosis**

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**SUBJECT:**
West Nile Virus (WNV) Infection and Laboratory Diagnosis

**ISSUE:**
Interpretation of laboratory test results from patients with suspected WNV infection

**BACKGROUND:**
A recent medical evaluation and initial laboratory studies of a Marine from Cherry Point, North Carolina, raised suspicion for what would have been the first case of symptomatic WNV infection in an active duty person. Clinical signs and symptoms, together with laboratory confirmation are important in making the diagnosis of WNV infection. Correct interpretation and reporting of laboratory studies is paramount, so that erroneous information is not provided to the Line Command. The laboratory results of active duty military personnel may be significantly different from civilians due to travel and immunization history.

**WEST NILE VIRUS:**
West Nile Virus is a single-stranded RNA virus in the family *Flaviviridae*, genus *Flavivirus*, and is a member of the Japanese encephalitis virus serocomplex, which contains several medically important viruses, including Japanese encephalitis, St. Louis encephalitis, Murray Valley encephalitis, and Kunjin virus; all are associated with human encephalitis.

Diagnosis of WNV infection is based on a high index of clinical suspicion and obtaining specific laboratory tests.

- WNV, or other arboviral diseases such as St. Louis encephalitis, should be strongly considered in adults ≥50 years who develop unexplained encephalitis or meningitis in summer or early fall.
- The local presence of WNV in animals, and other human cases should further raise clinical suspicion.
- Obtaining a recent travel history is important in clinical decision-making.
- Severe neurological disease due to WNV infection has occurred in patients of all ages, and year-round transmission is possible in some areas. Therefore, WNV should be considered in all persons with unexplained encephalitis and meningitis.

## CLINICAL PRESENTATION:

### Mild WNV infections

Most WNV infections are mild and often the infection may be clinically unapparent.

- Approximately 20% of those infected develop a mild illness (West Nile fever).
- The incubation period is thought to range from 3 to 14 days.
- Symptoms are generally present for 3 to 6 days.

When presenting as a mild infection, reports from earlier outbreaks of WNV infection have described a febrile illness of sudden onset often accompanied by the following:

1) Malaise
2) Headache
3) Anorexia
4) Myalgia
5) Nausea
6) Rash
7) Vomiting
8) Lymphadenopathy
9) Eye pain

The full clinical spectrum of West Nile fever as it presents in the United States has not been determined.

### Severe WNV infections

Approximately 1 in 150 infections will result in severe neurological disease.

- The most significant risk factor for developing severe neurological disease is advanced age.
- Encephalitis is more commonly reported than meningitis.

In recent outbreaks, the following symptoms occurred among patients hospitalized with severe disease:

1) Fever
2) Gastrointestinal symptoms
3) Weakness
4) Change in mental status

- A minority of patients with severe disease developed a maculopapular rash or small red papules involving the neck, trunk, arms, or legs.

- Several patients experienced severe muscle weakness and flaccid paralysis.
- Neurological presentations included:

    1) Ataxia and extrapyramidal signs
    2) Cranial nerve abnormalities
    3) Myelitis
    4) Optic neuritis
    5) Polyradiculitis
    6) Seizures

Although not observed in recent outbreaks, myocarditis, pancreatitis, and fulminant hepatitis have been described.

**LABORATORY DIAGNOSIS:**

The most efficient diagnostic method is detection of IgM antibody to WNV in serum or cerebral spinal fluid (CSF) collected within 8 days of illness onset using the IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA). Since IgM antibody does not cross the blood-brain barrier, IgM antibody in CSF strongly suggests central nervous system infection.

The following is the minimal information required when submitting specimens to be tested (timing is very important in interpretation of results):

1) Patient's name, address, age, and sex
2) Physician's name, address, and telephone number
3) Date of onset of patient's illness
4) Type of specimen collected
5) Date of specimen collection
6) Clinical signs and symptoms of patient

Further information regarding specific state requirements for data collection and submission can be found in the links at the following website:
http://www.cdc.gov/ncidod/dvbid/westnile/city_states.htm

**Serological Studies**

The close antigenic relationship of the flaviviruses, particularly those belonging to the Japanese encephalitis complex, accounts for many serologic cross-reactions observed in diagnostic evaluation.

Positive IgG results to St. Louis Encephalitis (SLE) and WNV indicate a possible prior infection with one or more of these Flaviviruses at some undetermined time. The Marine in question had positive IgG antibodies to WNV and SLE, indicating a possible prior infection.

Positive IgM results can be considered presumptive evidence of recent infection. The Marine had negtive IgM results, making the likelihood of recent infection highly improbable.

Convalescent sera can later be used to confirm acute infection if both the IgG and IgM antibody screening is positive for WNV. If both tests are positive, the data is considered presumptive evidence of recent infection with WNV or a closely related flavivirus such as SLE. Further testing of convalescent sera is necessary to confirm this diagnosis. There is no indication to obtain convalescent cerebrospinal fluid. This question was asked of two state health laboratories regarding the further evaluation of the Marine. (Trying to get an individual to undergo a lumbar puncture when he/she is well has the potential to do harm and does not provide the type of sample necessary for testing).

Further complicating the interpretation of serology studies is that sera of patients who have been recently vaccinated against related flaviviruses (e.g., yellow fever and/or Japanese encephalitis) may have positive IgG results in the initial screening due to cross-reactivity. Positive IgG results in this setting may be the result of effective immunization and not prior infection. Previous infection with another flavivirus (e.g., dengue fever and/or SLE) can also cause the initial IgG screening to have a positive titer. Recent blood transfusions can also produce positive screens, depending upon the infection history of the blood donor. The Marine in question had received yellow fever vaccine, and the North Carolina State Laboratory, reported he also had a prior infection with dengue fever.

In summary, preliminary laboratory data must be interpreted with caution and correlated with the patient's clinical presentation and past medical, travel, transfusion, and vaccine history.

**(NOTE: WNV IgM class antibody has also been shown to persist for over a year post-infection in some patients).**

The laboratory concluded that the Marine did not have WNV infection, and the positive IgG titer was most likely due to cross-reactivity with his response to yellow fever immunization and prior dengue infection.

**REFERENCES:**

http://www.cdc.gov/ncidod/dvbid/westnile/index.htm